BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson’s disease

T Foltynie, B Cheeran, C H Williams-Gray, M J Edwards, S A Schneider, D Weinberger, J C Rothwell, R A Barker, K P Bhatia

ABSTRACT

Background: Levodopa induced dyskinesias (LID) are a common problem which ultimately limit the effective treatment of patients with Parkinson’s disease (PD). There is accumulating evidence that LID develop due to abnormal synaptic plasticity, which is in turn influenced by the release of brain derived neurotrophic factor (BDNF).

Methods: The influence of a common functional polymorphism of the BDNF gene on the risk of developing dyskinesias in a large cohort of patients with PD (n = 315), who were independently and variably treated with levodopa and/or other dopaminergic treatments, was investigated.

Results: Patients with the met allele of BDNF, associated with lower activity dependent secretion of BDNF, were at significantly higher risk of developing dyskinesias earlier in the course of treatment with dopaminergic agents (hazard ratio for each additional met allele 2.12, p = 0.001), which persisted following adjustment for potential confounding variables.

Conclusion: This functional polymorphism may help predict which individuals are most at risk of LID and is consistent with the known actions of BDNF on synaptic plasticity in the striatum.

A common complication of dopaminergic therapy in Parkinson’s disease (PD) is levodopa induced dyskinesia (LID), which will affect approximately 20–45% of patients with PD who have been receiving levodopa for 5 years. LID can be disabling, and are a major determinant of quality of life and health care costs in PD. There is substantial variability in the time from levodopa initiation to LID onset and several risk factors have been established for the earlier onset of LID, which include younger age, greater disease severity at baseline and higher daily levodopa dose but these factors do not explain all of the variability observed in time to LID onset. LID are hypothesised to be a consequence of aberrant neuroplasticity in corticostratial synapses caused by long term non-physiological dopaminergic stimulation of striatal neurons. Thus the propensity to develop LID under such circumstances may relate to individual variations in factors that control plasticity. The present investigation focused on a common functional polymorphism in the brain derived neurotrophic factor (BDNF) gene, in which the minor allele (val66met) has a frequency of 16–25%. BDNF was first discovered in 1982 and has been postulated to have a number of actions, including a major role as an activity dependent neuromodulator. Both BDNF itself (through its high affinity receptor TrkB) and its secreted precursor form proBDNF (through its high affinity receptor p75NTR) are known to modulate synaptic transmission by regulating synapticogenesis and synaptic plasticity and efficacy. The presence of the minor allele (val66met) leads to reduced depolarisation induced secretion of BDNF from neuronal cells. Indeed, compared with val homozygotes, subjects with met alleles have less change in cortical motor maps in response to motor training and less response to repetitive transcranial magnetic stimulation plasticity and metaplasticity probes in healthy subjects based on our own unpublished observations. In addition, BDNF is known to modulate several of the receptor systems and molecular pathways implicated in the development of LID (eg, D1 and DARPP-32, D3 receptors, N-methyl D-aspartate (NMDA) receptor subunit expression and GABAergic receptors). Previous studies have examined the possible role of BDNF polymorphisms in the pathogenesis of PD given its established role as a trophic factor for dopaminergic neurons. Although two studies in far eastern populations have found such an association, this has not been consistently reproduced in other populations of patients with PD. The present study however investigated a different role for BDNF. Taking into account its critical role in activity dependent modulation of synaptic plasticity and increasing evidence that the val66met polymorphism functionally influences this role, we hypothesised that this polymorphism could influence the time to develop LID in a large cohort of patients with PD.

METHODS

All patients were seen and assessed at the Cambridge Centre for Brain Repair in Cambridge, UK, as part of an ongoing study of PD. Follow-up assessments were performed every 1–2 years, if necessary with community visits to the patients’ own homes to maximise complete data collection. Each patient was assessed according to a standardised protocol, including details regarding dates of symptom onset and diagnosis, dates of medication use, family history, and past medical and social histories, and then examined by a neurologist with an interest in movement disorders. All patients were assessed with the Unified Parkinson’s Disease Rating Scale (UPDRS) (which incorporates dyskinesia assessment) and a battery of cognitive assessments. Patients’ medications were not adjusted as part of attendance at this clinic. All patients were UK Caucasians apart from one Afro-Caribbean
individual, two Asian–Indian individuals and one individual who was half Caucasian and half Asian–Indian.

Only patients meeting UK Parkinson’s Disease Society Brain Bank criteria for the diagnosis of PD were included in this study. To maximise the accuracy of recording the presence/absence and date of onset of LID, only patients who were free of LID at the time of their first assessment were included. As LID may also be induced by dopaminergic agonist drugs, doses of all dopaminergic medications were noted at the first patient assessment and converted to equivalent levodopa doses using the following formula. Equivalent levodopa dose = (levodopa \times 1.2 if COMT inhibitor) \times 1.2 if 10 mg selegiline OR \times 1.1 if 5 mg selegiline) + (pramipexole \times 400) + (ropinirole \times 40) + (caberline \times 160) + (pergolide \times 200) + (bromocriptine \times 10) + (lisurdle \times 160), all doses in mg. This allows a comparison between patients on different dopaminergic regimens and takes account of the risk of dyskinesia that exists from both levodopa and to a lesser extent from dopamine agonist use.\(^6\)\(^7\)

Ethics approval for the study was granted by the Cambridge Research Ethics committee. All patients provided written consent for genetic analysis of their DNA, extracted using standard techniques from peripheral blood samples. Genotyping for BDNF val66met genotypes was performed by a 5’ exonuclease allelic discrimination Taqman assay.\(^6\)\(^7\) All statistical analysis was performed using Stata V.8.0. Baseline demographic and clinical variables were compared across genotypic subgroups, using analysis of variance for continuous variables and \(\chi^2\) analysis for categorical variables. A survival analysis was performed with date of initiation of dopaminergic treatment used as baseline and censoring occurring at (1) onset of LID or (2) latest date of follow-up assessment if free from LID.

**RESULTS**

A total of 315 patients attending the Cambridge Centre for Brain Repair clinic were free from LID at their first assessment and had reliable data regarding date of initiation of dopaminergic medication. Table 1 shows a description of these patients, divided according to their BDNF genotype (confirmed to be in Hardy–Weinberg equilibrium). Analysis of variance found no significant differences between BDNF genotypes in patients, with respect to gender, age at diagnosis, duration of disease at first clinic attendance and UPDRS motor scores. Similarly, there was no significant difference between genotypic groups in mean L-dopa equivalent dose at the time of censoring.

At the time of analysis, 47 patients had developed new onset of LID having been dyskinesia free when first assessed in the clinic, 21/190 val/val patients, 21/112 val/met patients and 5/13 met/met patients. Figure 1 shows Kaplan–Meier curves for the development of LID for each BDNF genotype from time of initiation of dopaminergic treatment. Calculating scaled residuals confirms that the proportional hazards assumption is met, and univariate Cox regression analysis produces a hazard ratio of developing dyskinesia of 2.12 (95% confidence interval (CI) 1.56 to 3.38) for each additional met allele (\(p=0.001\)). Multivariate Cox regression analysis with adjustment for possible confounding variables (age at diagnosis, gender, total UPDRS score at baseline, duration of follow-up and equivalent L-dopa dose at censoring) increased the hazard ratio for developing dyskinesia to 2.21 (95% CI 1.36 to 3.59) (\(p<0.001\)) for each additional met allele.

**DISCUSSION**

In this study we have shown a significant difference in time to onset of LID between patients with PD according to their BDNF val66met genotype, with val/met homozygotes having the longest time to onset of dyskinesia, heterozygotes midway and met/met homozygotes developing dyskinesia earliest. In our study, as in all previous studies, met homozygotes are rare (4%) while val homzygotes and val/met heterozygotes are common (60% and 36%, respectively).

As far as possible, we tried to ensure that our patients had accurate data recording of the date of onset of their PD, the date of dopaminergic drug initiation and the date of their dyskinesia. Inevitably, for many patients we relied on retrospective dates for dopaminergic drug initiation but have no reason to suspect that there should be differential recall bias between genotypic subgroups. We made no systematic adjustment to medications during this study, as pharmacological interventions were all performed by neurologists or physicians, independent of this study and unaware of their patients’ BDNF genotype. As a result, patients were exposed to varying regimens of PD therapies at different times, which were determined by clinical
need. The relationship between dopaminergic replacement and LID risk may depend on many factors, including the rate of dose escalation, maximum daily dose administered, cumulative dose of drug, duration of drug exposure or pattern of drug administration throughout the day. As far as we were able, we adjusted for the possible effect of dopaminergic medication as a potential confounder in this analysis and we do not believe that the findings here are explicable simply in terms of prior differential medication use. Furthermore, multivariate analysis with adjustment for possible confounding factors (age at diagnosis, gender, UPDRS motor scores, equivalent levodopa dose at latest follow-up/onset of LID and duration of follow-up) increases the association between BDNF val66met genotype and risk of development of LID.

The mechanism by which dopaminergic treatments lead to dyskinesias has been the subject of much research and discussion, but there is an emerging consensus that LID is the result of aberrant plasticity within the denervated striatum in response to non-physiological pulsatile stimulation with dopaminergic drugs. This leads to overactivity of the striatal output pathways via alterations in the sensitivity of striatal glutamatergic receptors. However, the exact processes leading to LID are still poorly understood. There is thought to be a sensitisation process, known as priming, which is caused by dopaminergic therapy, and is thought to result from the intermittent nature of the drug administration and the non-selective way in which dopamine receptors are stimulated.

BDNF genotype could influence this process in that lower perisynaptic BDNF levels in val/met and met/met individuals cause a reduction in synaptic plasticity in corticostriatal synapses (and also seen in our own unpublished observations). It has been demonstrated that mature BDNF facilitates synaptic potentiation through the TrkB receptor, whereas proBDNF facilitates synaptic depression through the p75(NTR) receptor. L-dopa treated parkinsonian rats that develop dyskinesia have altered synaptic plasticity in that they fail to depotentiate corticostriatal synapses in response to low frequency stimulation in contrast with non-dyskinetic parkinsonian rats. It is thus tempting to hypothesise that BDNF levels influence corticostriatal synaptic plasticity in patients with PD that carries with val alleles able to potentiate and depotentiate corticostriatal synapses more effectively than met allele carriers, who thus develop a pathological storage of information that would normally be erased, leading to the development of abnormal motor patterns (ie, dyskinesias).

A second possibility is that BDNF genotype might influence the onset of dyskinesias via an effect on the background level of dopamine release and D1 stimulation. BDNF is known to stimulate dopamine release in the hippocampus in a dose dependent fashion, which can be blocked by antagonists to the BDNF receptor TrkB. Furthermore, BDNF is known to induce a dopaminergic neuronal phenotype in embryonic cell culture and inhibition of BDNF causes loss of nigral dopamine neurons. BDNF can also upregulate D1 receptors both in neural cell lines and in a mouse model of PD. It follows therefore that higher BDNF levels (val/val patients) may lead both to a greater background level of dopamine release and D1 receptor stimulation, and together this reduces the overall intermittent or pulsatile pattern of dopamine stimulation that occurs with dopamine replacement therapy.

In conclusion, this study suggests that patients with PD with the BDNF met alleles are at risk of developing LID earlier in the course of their disease than val/val homozygotes. Further research is needed to confirm these results in additional populations of patients with PD, and to elucidate the pathophysioblogical mechanisms that might underlie this. However, if the development of disabling dyskinesias can be shown to be related to the presence of one or two met alleles, then this could have implications for the treatment of patients with PD. Already dopamine agonists are used in preference to L-dopa, especially in the early stages of disease in younger patients, and this might be particularly important in patients with met alleles. Alternative agents such as NMDA antagonists or adenosine A2A antagonists might also be preferable in patients with met alleles, especially met homozygotes. The early use of alternative approaches such as non-pulsatile levodopa administration (intrajejunal levodopa gel), subcutaneous apomorphine or deep brain stimulation, could also be considered earlier in patients with met alleles. Such treatments are currently restricted until late in the disease process according to current guidelines. Further work to develop therapies for PD whether neuroprotective, neurorescuing or designed to delay LID might also include methods of administering BDNF or agonists for the TrkB or p75(NTR) receptors.

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